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New insights in atrial remodeling

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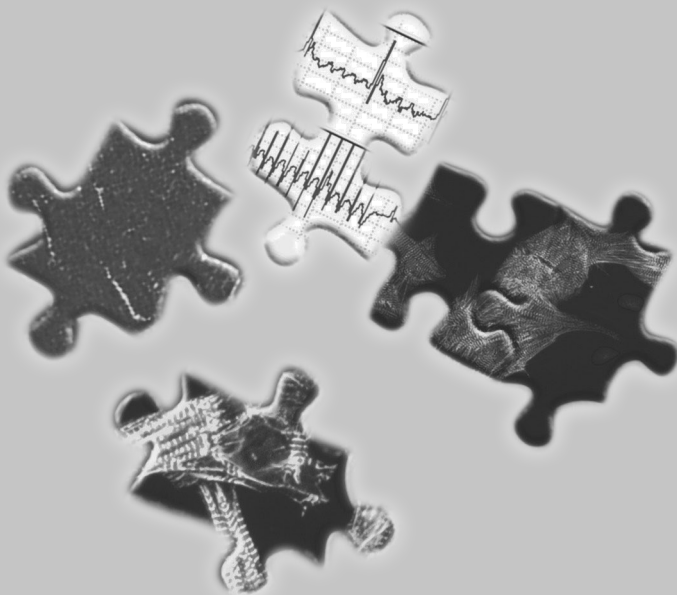
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Summary

Nederlandse samenvatting

Dankwoord

Biography



Summary

Atrial fibrillation is the most common cardiac arrhythmia. At present, in Europe, more than 6 million people suffer from atrial fibrillation. With aging of the population the incidence of atrial fibrillation is expected to increase. Risk factors for atrial fibrillation include older age, hypertension, diabetes, valve disease and heart failure. Although atrial fibrillation occurs without the presence of an underlying disease, most often a concomitant disease is present. Over time, atrial fibrillation tends to become more persistent, which is both due to the presence of the arrhythmia as well as the presence and progression of concomitant diseases. Atrial fibrillation is not directly life-threatening, but is it not benign, consequences of atrial fibrillation include an increased risk of stroke, heart failure, hospitalizations, increased mortality and an impaired quality of life.

Atrial fibrillation is a complex disease and the pathophysiology underlying the arrhythmia is diverse. Studying the processes occurring before the actual arrhythmia takes place may give insight in the mechanisms of development of atrial fibrillation and may improve prevention. An important aspect of atrial fibrillation is atrial remodeling, referring to changes, either electrical, contractile or structural, which take place in the atria upon a demanding situation. Structural remodeling consists of atrial enlargement, hypertrophy, fibrosis, dedifferentiation and cell death. Although initially beneficial, remodeling might result in decompensation and reduced cardiac function. Atrial remodeling is not only caused by atrial fibrillation, but also by underlying diseases, such as hypertension or heart failure, and might therefore already start before onset of atrial fibrillation. Atrial remodeling increases the susceptibility for and the progression of atrial fibrillation. One factor inducing remodeling is stretch, which occurs due to underlying heart diseases.

In addition to known factors involved in the pathophysiology of atrial fibrillation also previously unrecognized mechanism might be involved. Even though it has been recognized long ago that atrial fibrillation increases the risk of stroke, the effects of activated coagulation on atrial remodeling have not been studied before.

The aim of this thesis was to investigate atrial remodeling *in vitro* and *in vivo*. We investigated atrial remodeling occurring before, induced by underlying diseases such as hypertension or heart failure, and after start of atrial fibrillation. Different factors inducing remodeling were studied, stretch, which is induced by underlying cardiac diseases, but also by atrial fibrillation itself, and a newly discovered pathway, activation of coagulation. In **Chapter 1** a general introduction is given and the background of this thesis is discussed.

In **Chapter 2** different aspects of structural remodeling are reviewed, as seen in patients with atrial fibrillation and in animal models. We focus on mechanical stretch, downstream signals of stretch, and their contribution to atrial fibrillation and structural remodeling. Structural remodeling is related to the severity of the underlying disease and duration of atrial fibrillation. In animal models an uncontrolled ventricular rate seems important in mimicking the clinical situation of atrial fibrillation in association with underlying heart diseases.

Because underlying cardiac diseases are an important factor in atrial fibrillation occurrence, atrial fibrillation progression and atrial remodeling, we investigated the effects of stretch *in vitro* and *in vivo*. In **Chapter 3** we aimed to develop an atrial cell culture model mimicking remodeling due to atrial pressure overload. Therefore neonatal rat atrial cardiomyocytes were subjected to cyclical stretch. We found activation of immediate early genes, which is an early response to stress, changes related to hypertrophy and dedifferentiation, including involvement of calcineurin signaling, cell death, and changes in expression of several potassium channels. This model can be used to investigate mechanisms involved in the remodeling process and to assess the effectiveness of new pharmaceutical compounds on remodeling induced by stretch.

In **Chapter 4** and **Chapter 5** a mouse model was used to investigate the effects of ventricular pressure overload in the atria. We used the transverse aortic constriction (TAC) model, an established model of ventricular hypertrophy progressing towards heart failure. First, in **Chapter 4**, we studied the changes in the atria upon ventricular pressure overload, and the effect of the angiotensin II receptor blocker losartan on the pressure overload induced atrial remodeling. We observed changes in atrial gene expression related to hypertrophy, fibrosis, and inflammation. In our study, losartan treatment during persistent pressure overload did not affect gene expression related to fibrosis or inflammation. Although atrial hypertrophy was still present, gene expression related to hypertrophy was reduced in mice treated with losartan.

Thereafter, in **Chapter 5**, in the same ventricular pressure overload model, we show development and progression of the atrial substrate after four and eight weeks of pressure overload. After four weeks only minor changes were observed in the atria, eight weeks of pressure overload induced significant atrial remodeling. We observed hypertrophy, not only at the mRNA level, but we also observed an increased atrial weight and increased atrial diameter. While gene expression related to fibrosis was increased, histologically, an increase in fibrosis was not observed. Furthermore, changes in expression of genes related to inflammation were observed and minor changes related to electrical remodeling were seen. In addition, atrial fibrillation could be induced, but no differences between the experimental groups were found. Interestingly, the extent of remodeling was directly related to the left ventricular end diastolic pressures.

Besides known factors involved in remodeling, such as stretch, also other previously unknown factors might be importantly involved in the remodeling process. One such factor might be activated coagulation, of which the roles in pathophysiological processes are more and more recognized. In **Chapter 6** the effects of activated coagulation factors thrombin and Factor Xa on cellular processes in both atherosclerosis and atrial fibrillation are reviewed. In addition, the potential implications of direct Factor Xa or thrombin inhibition outside the effects on coagulation are discussed.

Subsequently, in **Chapter 7**, we aimed to study the effects of activated coagulation on atrial cells and we investigated whether inhibition of coagulation could attenuate the remodeling process in goats with atrial fibrillation. Stimulation of atrial fibroblasts with

thrombin induced increased collagen synthesis, increased expression of inflammatory genes and smooth muscle actin. The latter indicating differentiation towards myofibroblasts. These changes could be attenuated by treatment with the direct thrombin inhibitor dabigatran. These changes were most likely mediated via protease-activated receptor (PAR)1. In addition, in goats with atrial fibrillation, treatment with nadroparin (targeting Factor Xa and thrombin) could attenuate atrial fibrosis and the complexity of the substrate for atrial fibrillation.

Finally, in **Chapter 8**, we discuss the use of experimental models to study remodeling in the setting of underlying diseases and we discuss potential new mechanisms in the remodeling process of atrial fibrillation, with a focus on stretch and on the coagulation system, while referring to the results presented in this thesis.